Biologics & Biosimilars: *Pharmaceutical Industry Questions*

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Outline of Presentation

- Definitions & Terminology
  - What is a Biological Medicine?
  - What is a Biosimilar Medicine?
  - What does Biosimilarity mean?
  - What is a Reference Substance and Reference Medicinal Product?
- Biosimilar Development
- Comparability Concept
- Considerations for choice of Reference Medicinal Product
- Specifications
- Comparison of requirements for registration of a Biosimilar and Reference Medicinal Product
- Totality of Evidence
- Questions from Industry

What is a Biological Medicine?

All medicines that contain a living organism, or are derived from a living organism or biological processes are considered Biological Medicines. They include, but are not limited to the following:

- Plasma-derived and animal products, e.g. Clotting factors, Immunosera, Antivenoms;
- Vaccines;
- Biotechnology-derived medicines (rDNA products) e.g. rHu-antihaemophilic factors, hormones(insulin, growth hormone, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids;
- Products developed for Human Gene therapy.

What is a Biosimilar Medicine?

A biosimilar is a biological medicine that is similar, but not necessarily identical, in terms of quality, safety and efficacy to an already registered reference biological medicine.

What does Biosimilarity mean?

Means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically **inactive** components; and

- there are **no clinically meaningful differences** between the candidate biosimilar product and the reference product in terms of safety, efficacy, purity and potency.

What is a Reference Substance and Reference Medicinal Product?

Reference substance:

- The active ingredient from the reference medicine that will be used in comparisons of physico-chemical characterization, and other properties, of the biosimilar.

Reference medicine:

- The comparator for head-to-head comparability studies with the biosimilar product in order to show similarity in terms of quality, safety and efficacy.
- It is the originator **medicine** (innovator product).
- Only an innovator product that was registered by SAHPRA in South Africa on the basis of safety, efficacy and quality can serve as a reference medicine.
- The reference product that is registered in South Africa must be sourced from a country that SAHPRA aligns itself with.
- It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

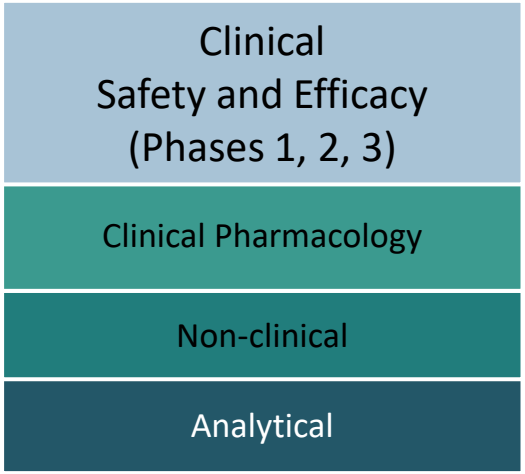
- *Note*: **A Biosimilar product may not be evaluated against more than *ONE* reference product.**

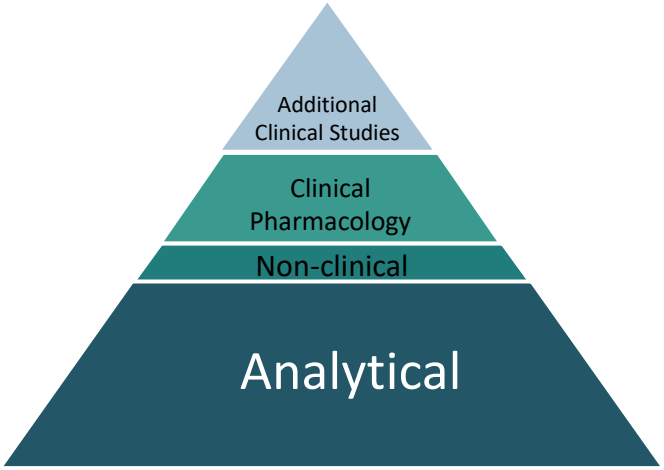
Biosimilar Development

Goals of "Stand-Alone" and Biosimilar Development are Different

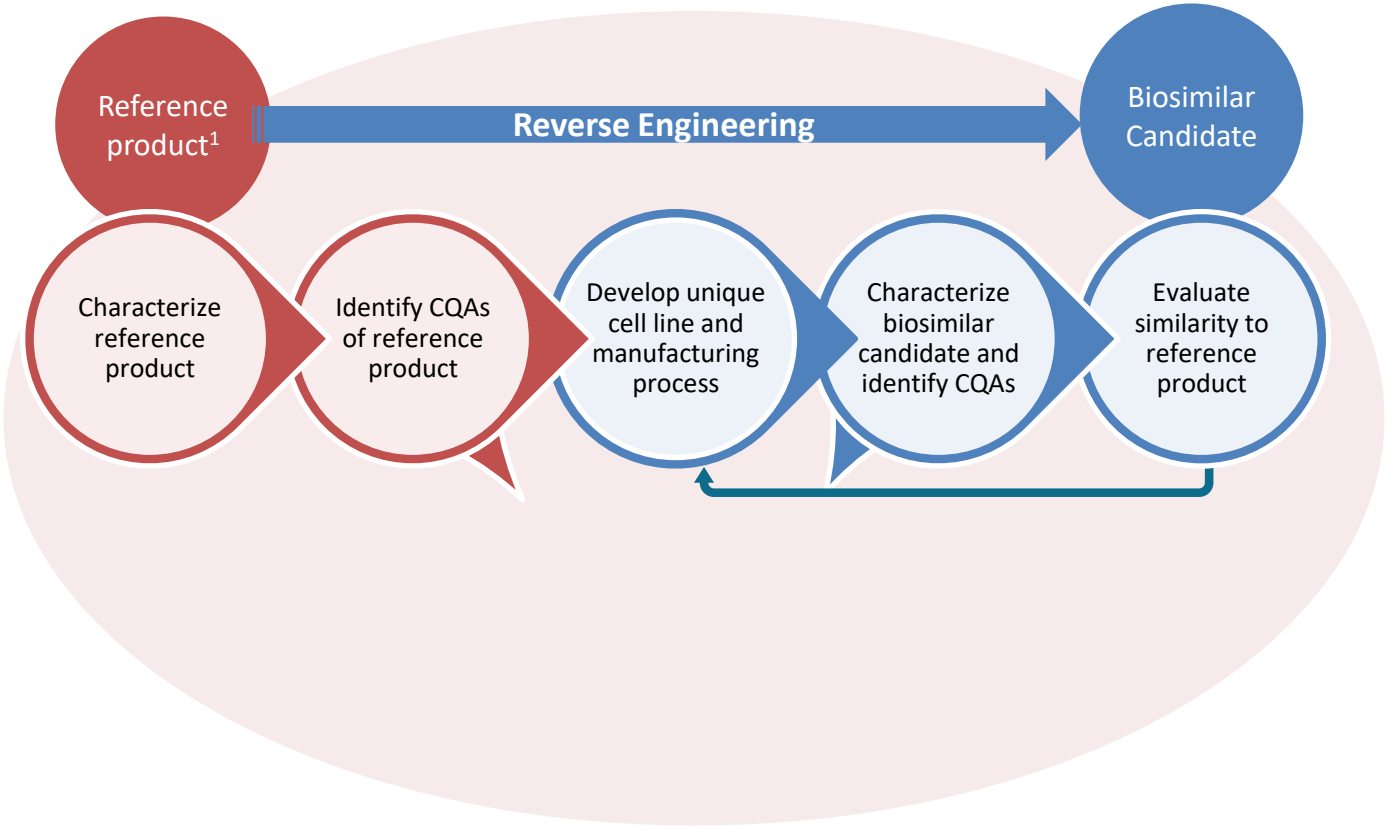
"Stand-alone" Goal: To establish safety and efficacy of a new product

"Biosimilar" Goal: To demonstrate biosimilarity





Biosimilars Are Reverse Engineered



1. Kozlowski S. *US FDA Perspectives on Biosimilar Biological Products*. 2014; Rockville, MD. Accessed February 6, 2017.
2. US Food and Drug Administration. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. Guidance for Industry.* Published April 2015. Accessed February 6, 2017.

Comparability Concept

- Comparability studies are needed to generate evidence substantiating the similar nature i.t.o. quality, safety and efficacy of the biosimilar and RMP.
- A stepwise approach is recommended during the development of a SBP:
  1. Analytical studies demonstrating that the biosimilar product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
  2. Animal studies (including the assessment of toxicity); and
  3. A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate comparative safety, quality, and efficacy in **ONE** or more registered indications for which the reference product is approved.
  4. The extent and nature of non-clinical & clinical studies to be performed depend on **the level of evidence** obtained in the physicochemical and biological characterisation studies.

Considerations for choice of Reference Medicinal Product

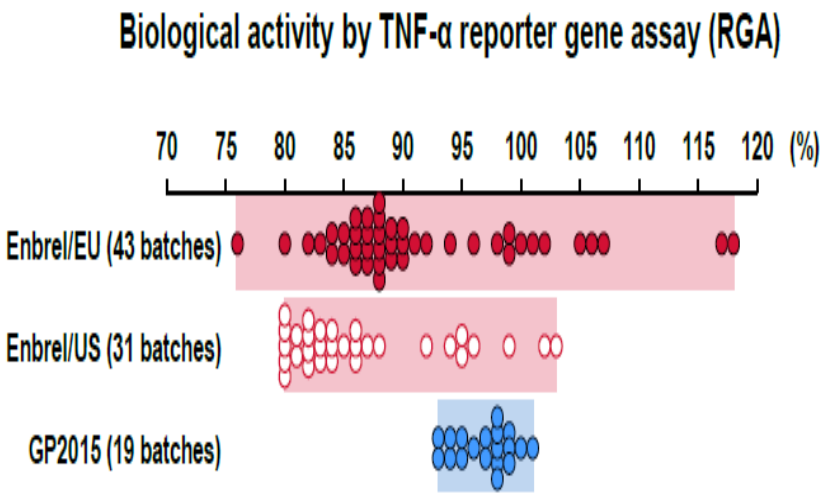
- The reference product should be the market leader and have been marketed for a sufficient period of time (≥ 5 years) and, hence, have a safety record.
- SA accepts foreign reference but only if procured from ICH countries (strong regulatory authorities).
  - No bridging studies are required between a foreign reference & SA reference product.
- The reference product must have been registered on a full dossier – a biosimilar cannot serve as a reference product.

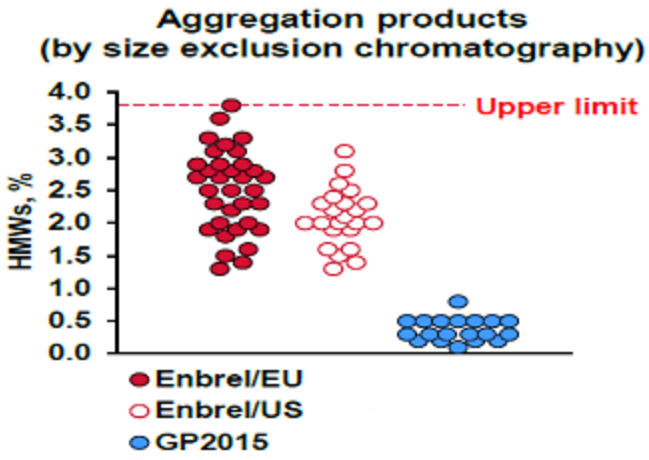
Reference Medicinal Product (cont.)

- The same reference product, procured from the same market, must be used throughout the development of the SBP and **several batches must be used.**
- The dose, dosage form and same route of administration must be used for the SBP as for the reference product and *ideally* the same formulation.
- A reference standard (WHO/Pharmacopoeial) cannot be used in the development of a SBP as it does not have a safety and efficacy record.

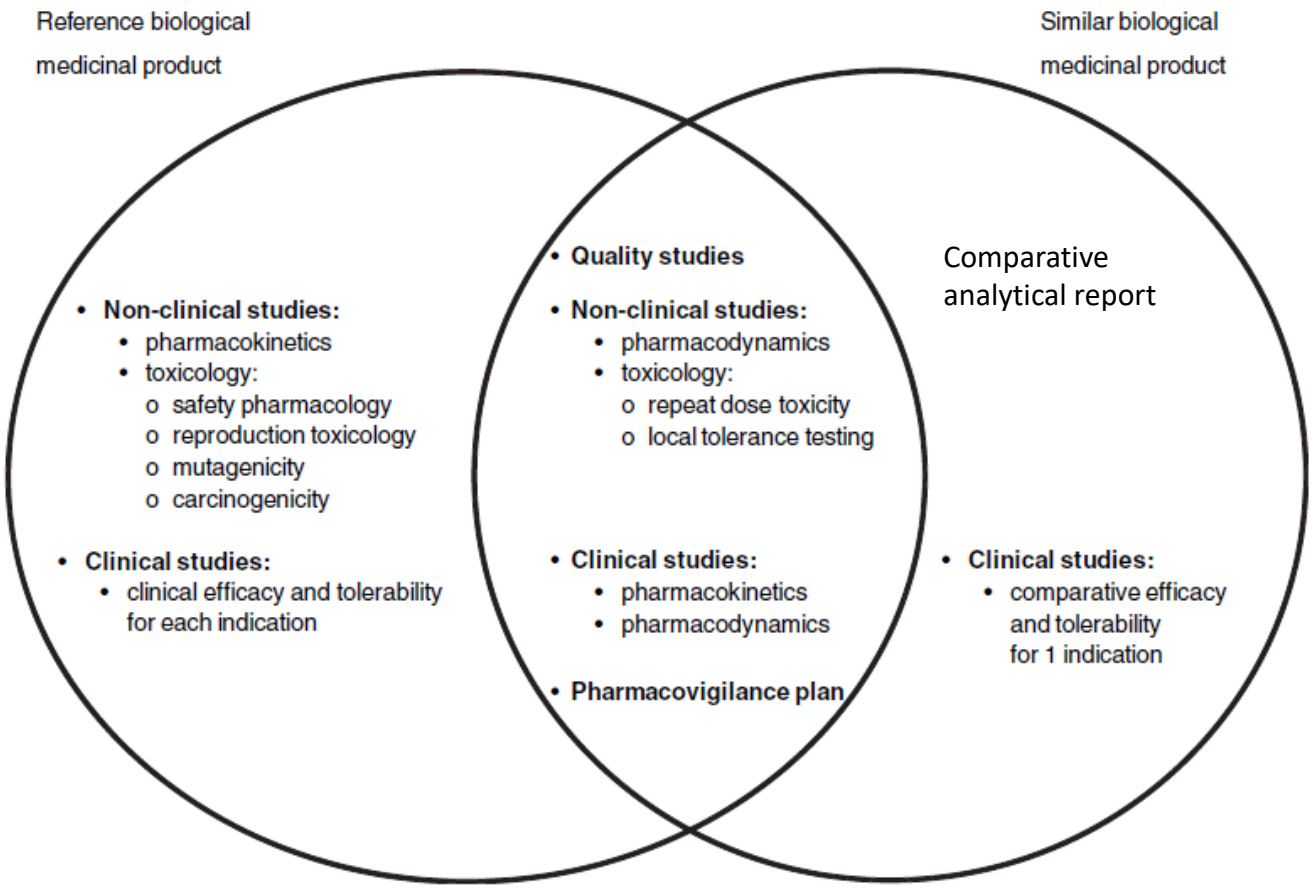
Specifications

- Specifications are chosen to confirm the quality of the drug substance and the drug product
- Acceptance criteria should be established and justified based on data obtained from:
  - Biosimilar batches used in clinical studies
  - Biosimilar batches used for demonstration of manufacturing consistency and biosimilarity, other relevant development data
  - Characterisation results from the reference product for the justification of specification acceptance limits for the biosimilar





Comparison of requirements for registration of a Biosimilar and Reference Medicinal Product

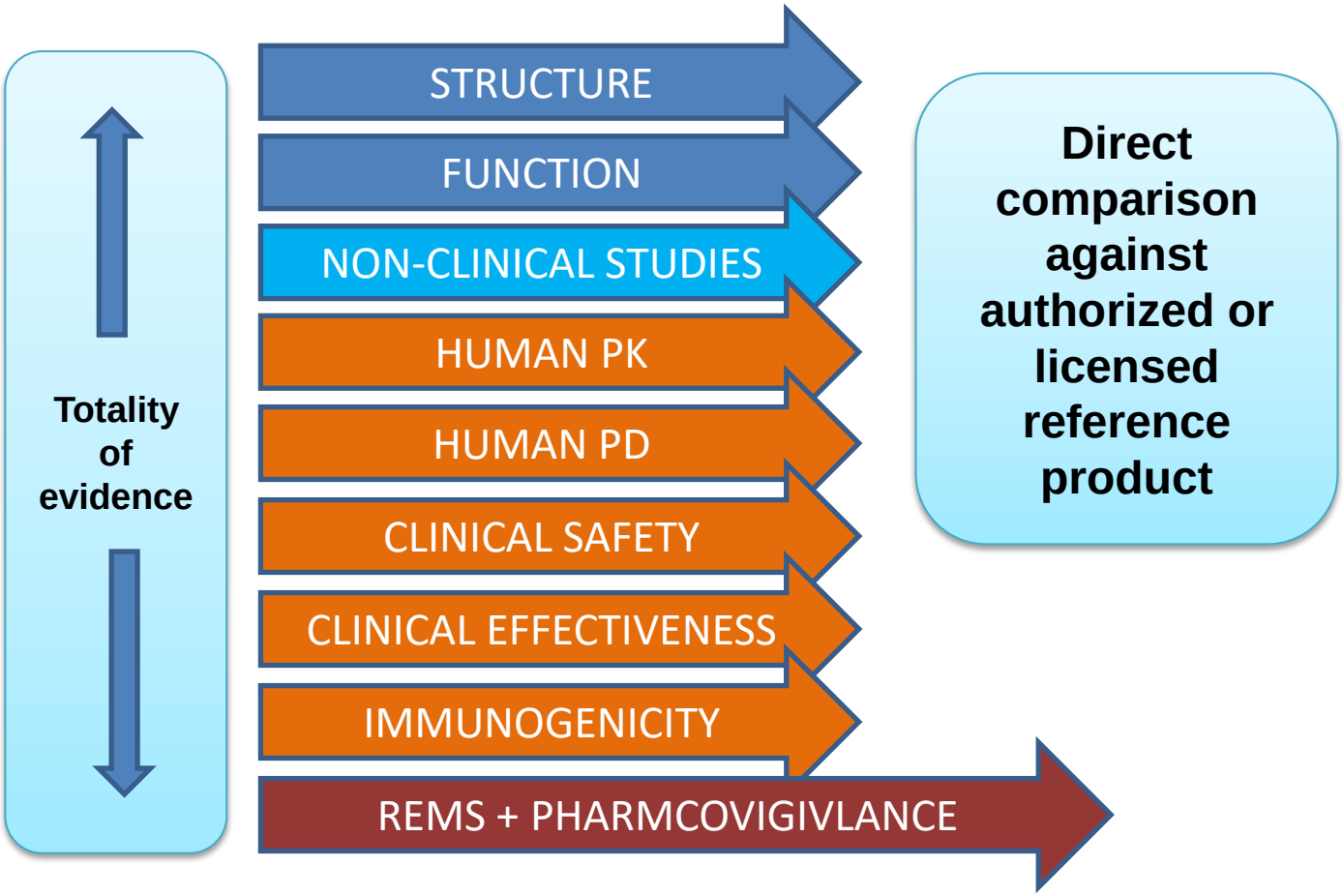


Totality of Evidence

→ **Recognize that the fundamental understanding of the originator drug is missing**

→ **In biosimilar development, the analytic package > clinical package**

→ **Drug appraisal based on totality of evidence (The Goal)**



PK = pharmacokinetics
PD = pharmacodynamics
REMS = Risk Evaluation and Mitigation Strategy

Industry Questions 1 & 2

1. The comparability report seems to be the first document that an evaluator will go to to get a quick overview of the submission. Where in the dossier should this be put? (the guideline does not say).

   Module 3.2.R.8 (Other).

2. How many different batches of API must be tested against the reference API during comparability studies? Or, put differently; is it acceptable to do all comparability studies on one only batch (the same batch) of the test API? (the guideline does not stipulate a minimum).

   Minimum of ~ 6 to enable statistical comparisons in the case of quantitative tests.

3. How many batches of reference product are required to establish the test product's final product specs? (the guideline does not stipulate a minimum)

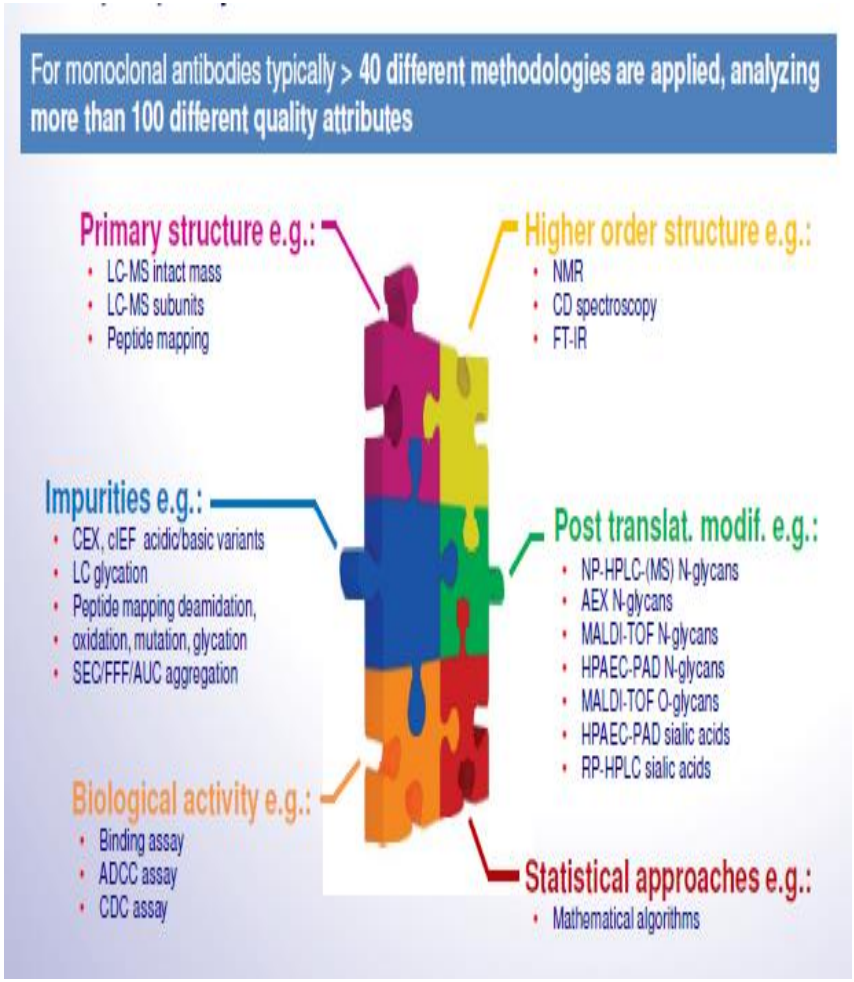
Since development of a biosimilar occurs over approximately 5 years it is important for the developer to obtain reference product batches at different stages of the development process since the reference product may be subject to amendments over that period. Many developers also use reference products from both USA and EU to account for genetic drift (or different manufacturing facilities). Hence over the development period it is not unusual for > 30 reference batches to have been used. However per comparative assay, ≥ 3 batches are used but this also depends on the complexity of the biological and whether it is a qualitative (SDS-PAGE) or quantitative (potency) test.

4. Which critical quality parameters (when found to be less similar than that of the test product) will determine the necessity for a full clinical study?

- Comparative clinical trials, (at least PK/PD for filgrastim/insulin), will always be necessary. Remember the goal of comparative clinical studies is to assess whether the biosimilar is different than the reference, not to demonstrate safety and efficacy. At the structural level, some differences are accepted to be present, for e.g., post-translational modifications (glycosylation), purity profiles (product-related), etc. However, if differences are observed at primary structure level (amino acid sequence) or a significant difference is observed in potency level (biobetter), then it may be likely that full clinical (and non-clinical) studies will be expected by the regulator. It is important to obtain the regulator's opinion first before planning clinical studies.

5. How many assays must have been used to establish each final product characteristic?

It depends on the product. For monoclonal antibodies, which are complex i.t.o. mechanisms of action, at least three. Others, such as Epo for potency, a mouse bioassay and/or an immunochemical assay (ELISA).



Industry Question 6

Must a SA innovator be used in above studies?

No

If not, are any bridging studies required (as e.g. comparative dissolution against a foreign innovator in the case of a biostudy done in support of a generic small molecule submission)?

No

According to the Biosimilar guideline, the reference product should be a product that is registered in South Africa and sourced from a country that MCC aligns itself with.

Yes

Could the Professor please give us some clarity regarding comparative testing with the reference product **sourced from South Africa**(i.e. are any additional characterisation studies required with the South African product if the reference product (in clinical studies) was obtained from another country).

If the reference product was sourced from the EU or USA, then it is not necessary to perform comparative physico-chemical studies against the SA registered product. It is neither a P & A nor BMC requirement.

Industry Question 7 & 8

7. What reference standards must be used in the standardisation / validation of assays, if not available commercially?

In-house reference

8. What are the stability data requirements at the time of submission? Accelerated studies are impractical for this type of product ….. is it a requirement?

Minimum data requirements as for NCE (12 months long term: 2 – 8 °C). Accelerated data at 25 °C/60 % RH for 6 months). Also, stress stability at 40 °C/75 % RH (although not necessary for shelf life but for determining degradation profile particularly in comparison to reference). Finally, temperature cycling studies to determine effect of a break in cold chain. Finally, in-use study of reconstituted and diluted product at room temperature.

Industry Questions 9 & 10

9. Is both a comparative PK / PD study and a clinical study (be it a small study) a requirement, or may a literature review be submitted in support of the clinical assessment of the product (if the product is already registered in another country)?

Not sure if I understand this question correctly. If the biosimilar is registered in another jurisdiction (EU/US), then same data must be submitted. Even if we should adopt a Reliance model, all data must still be submitted. In the case of simple biologics (insulin, filgrastim, i.e., non-glycosylated), then a simple Pk/PD study may suffice. For more complex biologics, a clinical study on at least one indication.

10. Is a comparative PK / PD study and a clinical study on the South African population, a necessity, or can it be done in another country?

Not a requirement.

Industry Questions 11 - 13

11. Can indications be extrapolated if not assessed in a clinical study?

Yes, if the underlying mechanism of action for other indications is the same; the same dose and same route of administration.

12. Does MCC have a specific naming convention for biosimilars?

No

13. Please comment on semi-synthetic active ingredients. The intermediate is manufactured by fermentation process (using working cell bank, cultivation and fermentation); the final API is then manufactured following chemical synthesis. Are there any special requirements for such products?

It is difficult to answer without examples. Antibiotics (e.g., amoxycillin) are semi-synthetic in that they are derived from 6-aminopenicillanic acid (6APA) obtained from fermentation and then chemically modified to produce, for example, acid resistant derivatives. Since these are relatively small molecules, they are not regarded as biologics. However, pegylated biologics (biologics that have been chemically modified by adding polyethylene glycol to its structures to prolong duration of action) are still regarded as biologics since it is the biological component that is responsible for its pharmacological effect. Examples are peg-interferon (Pegasys), filgratim (Neulasta), etc.

Industry Question 14

Insulin and antibiotics are not regarded as biologicals. Could the Professor please give some pointers / examples of other type of APIs that is not regarded as biologicals (e.g. semi-synthetic products – see point above).

Insulin is regarded as a biological (by BMC) and, hence, the biosimilar requirements apply for registration of "equivalents". Generally biologicals obtained by total chemical synthesis, i.e., those less than 50 amino acids, e.g., calcitonin (32 amino acids), oxytocin and vasopressin (9 amino acids), etc., are considered pharmaceuticals.

Industry Question 15

The last issue is post-registration amendments. The current amendment schedule is totally insufficient to address post-registration amendments to biological products. The (new) biological amendment guideline is not yet finalised. Could the professor please give some guidance on what (if anything) we should do in the meantime to correctly classify the variations

Amendments are reviewed by BMC. This has been a major issue for the committee and has led to the development of the current Amendments Guideline for biologicals. We have observed that amendments classified as Type A and B are in fact Type C amendments. The important thing though is that the data submitted support the change, i.e., that quality is not negatively affected.

Industry Question 16

For Clinical submissions, especially SR-PIN type amendments, should the SR-PINs code (CCC-SRN) be used or how should safety related amendments be differentiated to indicate a clinical safety change as opposed to a regular clinical update?

- *CCC-SRN -The code for a SR-PIN application/submission (SR-PINS)*
- *CPA- Package insert amendments for clinical aspects of registered/ old medicines (Regular clinical update)*

Industry Question 17

Is the fast track fee for clinical amendments applicable still for the Biological Unit?

Clinical Unit Response

The amended Act 101 does not make provision for fast-track applications.

[That said, fees are currently being reviewed by SAHPRA.]

Industry Question 18

What is the estimated timelines for review of a safety clinical update and for a regular clinical update by the Biological Department?

Clinical Unit Response

Judging by our clinical timelines, I would say an average of 2-3 months per application. With the backlog, 2-year waiting times have been experienced.

BMC Response

- *These are generally not evaluated by the Biological unit, but are considered by the Pharmacovigilance unit. Evaluations take place as soon as practical, depending on the expertise required for evaluation.*
- *The HCR for a biosimilar medicine should apply the safety update approved for the originator product, or justify to MCC/SAHPRA why this should not be required.*

Industry Question 19

Will approvals from RA of PICs countries or countries with whom the MCC aligns itself be considered by the Biological Department?

A guideline on Reliance mechanisms for registration of all medicine classes will be developed by SAHPRA.

Industry Question 20

Why is clinical data needed for well defined molecules?

I find it difficult to answer this question without knowing what the poser means by "well defined molecules."

- *–If the product is classified as a biosimilar then clinical data are required in accordance with the Biosmilars Guideline.*
- *–In the case of a **complex** biological (or non-biological) substance, e.g., enoxaparin (or other low molecular weight heparins), for which the clinical pharmacology has not been fully characterised then clinical data will also be required.*

Clinical Unit Response

There's still some confusion wrt well-known biological molecules as far as the clinical evaluations unit is concerned. I'm sure it would be safe to regard them as "generics" after enough experience has been obtained but, we're still not sure to what extent the seed lot and manufacturing processes differ from one seed lot batch to another in the so-called well-known molecules, and to what extent and / or in which direction that affects and / or shifts well-known clinical safety and efficacy parameters, respectively.

Industry Question 21

How relevant is the use of "totality of evidence" strategy when registering biosimilars?

This is the FDA approach and one we are striving towards. Currently, assessments are made by evaluators of three committees – P & A, BMC and CCC. However, the final recommendation to the CEO is made by the BMC.

Industry Question 22 & 23

22. What factors need to be considered when choosing a reference medicinal product?

See slides 9, 14 & 15

23. How are specifications set?

See slide 16

Industry Question 24

What are the criteria for Clinical and Non-Clinical data for vaccines?

- *I am not sure what they want here (Dr James Southern).*
- *For vaccines there is an emphasis on safety as these are given to healthy people (babies) and a sufficiently large data- base of exposed persons is important to reveal potential rare adverse events.*
- *There is also an important need for a post-marketing surveillance plan to provide additional safety data - particularly in special populations, infants, pregnant women, elderly etc.*

Industry Question 25

What are the evaluators looking for in “3.2.R.8 other” for Biosimilars?

The comparability report covering the analytical and in vitro biological studies performed on the candidate biosimilar and the Reference Medicinal Product

Industry Question 26

We would like to gain a better understanding of the process of Biosimilar registration from the start.

1. Which unit has the final say if there are disputes? *Committee of Chairs. But thusfar there has been no disputes.*
2. What parts of the dossier does the Biologics committee evaluate? *All Modules.*
3. Will there be any fast track/expedited review of Biosimilars? *A guideline on priority review is nearing completion and will be published on the website for comment – probably before June. The amended Act does not make provision for fast track review.*
4. If yes, what will the criteria be? Can the fee amount for review of clinical amendments be considered as fast track review by the Biological? *Fees for all activities that will be performed by SAHPRA are under review.*

Industry Question 27

As per Biological guidelines, Labelling changes and quality changes are included; does this mean that “clinical” and “P&A” amendments will be submitted directly to the Biological unit?

All amendments to biological medicines (P & A, PI/PIL) are reviewed by the BMC.

Industry Question 28

The type of submission for biologicals is different to the current amendment guidelines types e.g. Type A,B or C. is this change only for biologicals or should we expect a phase out of these types in the future update of the amendment guideline (e.g. Major Quality Change).

- *The MCC/SAHPRA guidelines for information to be supplied in support of amendments to registered biological medicines are based on the WHO guideline for amendments to licensed vaccines.*
- *Quality amendments to approved biosimilar medicines should follow the same guidelines.*
- *Safety amendment (labelling) should also consider the information provided by the originator medicine.*
- *These should not impact on the current approved guidelines for pharmaceutical medicines.*

Industry Question 29

Is it necessary to include the Clinical Committee codes due to the lack of Biological Codes for submission?

Clinical Unit Response

It's probably best to indicate some code in the absence of a Biological code. Even if to just ensure that it is routed for clinical review, be it biological or clinical.